

Applicant further responds to the Examiner's request that the term "signal amplifying" be clarified. Applicant notes that this term is one understood in the art, as evidenced, *inter alia*, by certain references made of record herein, including:

Urdea *et al.*, 1993, "Direct and quantitative detection of HIV-1 RNA in human plasma with a branched DNA signal amplification assay," *AIDS* 7(Supp.): S11-S14.

Urdea *et al.*, 1991, "Branched DNA amplification multimers for the sensitive, direct detection of human hepatitis viruses," *Nucl. Acids Research Symposium Series* 24: 197-200.

Applicant respectfully contends that these methods are competent detection methods for use in the practice of the claimed methods of the invention, and that the term "signal amplify" in the claims would be understood by those with skill in the art.

The amended claims are non-obvious over the cited prior art.

Claims 1-12, 21, 36, 37, 40, 41, 52 and 53 stand rejected under 35 U.S.C. §103 as being obvious over the teachings of Kopreski *et al.* in view of the teachings of Leitzel *et al.* Applicants respectfully traverse.

Applicants respectfully contend that the Office has not established the required *prima facie case of obviousness* based on the cited references. Applicants contend that what is missing is one of the requirements of obviousness: that one of ordinary skill have a reasonable expectation of success. *In re Vaeck*, 947 F.2d 448, 20 USPQ2d 1438 (Fed. Cir. 1991); MPEP §2143.02. Applicants contend that the biological arts are known to be unpredictable, and that detection in blood plasma or serum of a single species of RNA encoding one particular gene as cited in Kopreski *et al.* would imbue the skilled worker with absolutely *no* expectation that any other particular species of RNA encoding another gene would be detectable. In support of this contention, Applicants submit herewith a scientific journal article by Hasselmann *et al.* (2001, *Oncology Reports* 8: 115-118), submitted herewith. In this reference, published after Applicants filing date, the authors report that they could detect

tyrosinase RNA in plasma and serum (Table 1, p. 116). However, these workers were *unable* to detect other tumor-associated RNA species in these serum or plasma samples (such as gp100 RNA or MART-1 RNA), despite the expression and presence of both species in circulating cells from the cancer patients (*Id.*). There is absolutely no evidence of record to contradict Applicants' assertions, supported by the teachings of the Hasselmann reference, that the skilled worker would have had no reasonable expectation of success in detecting and particular RNA species in blood plasma or serum in view of the cited prior art. All that the primary reference contains is a general, unsupported suggestion that "other tumor RNA" would be detected in blood plasma or serum. There is no basis in the cited art that an attempt to detect any particular species of RNA in sera would be successful, and the Action points only to that single unsupported assertion in the primary reference to support its position that the skilled worker would have a reasonable expectation of success. This is insufficient. Although these references might be sufficient to make it obvious to try to detect RNA in sera, "obvious to try" is improper and is not the legal standard for establishing a *prima facie* case of obviousness. *In re O'Farrell* 7 USPQ 2d 1673 (Fed. Cir. 1988). In particular, the cited references lack any *evidence* that any species of RNA could be found in blood plasma or serum (other than the species disclosed in the primary reference), in contradistinction with the facts in *O'Farrell* that supported an obviousness rejection therein.

Applicants respectfully contend that the instant rejection under 35 U.S.C. §103 has been overcome by their argument herein. Withdrawal of this rejection and allowance of the claims is therefore respectfully solicited.

Applicant believes that all requirements of patentability have been fully met, and allowance of the claims is respectfully solicited.

If the Examiner in charge of this application believes it to be helpful, he is invited to contact the undersigned attorney by telephone at (312) 913-0001.

APR-15-03 10:15 From:

T-021 P.12/29 Job-022

Respectfully submitted,
McDonnell Boehnen Hulbert & Berghoff

By:

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Reg. No. 35,303

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"Marked-up" copy of amended claims

1. (Amended) A method for detecting tumor-derived or tumor-associated RNA in the plasma or serum fraction of blood from a human or animal, wherein the tumor-derived or tumor-associated RNA is epidermal growth factor RNA, epidermal growth factor receptor (~~erb-B-1~~) RNA, her-2/neu RNA, c-myc RNA, heterogeneous nuclear ribonucleoprotein A2/B1 RNA or any combination thereof, the method comprising the steps of:

a) extracting mammalian total RNA from plasma or serum, wherein a fraction of said extracted RNA comprises a tumor-derived or tumor-specific RNA species that is epidermal growth factor RNA, epidermal growth factor receptor (~~erb-B-1~~) RNA, her-2/neu RNA, c-myc RNA, heterogeneous nuclear ribonucleoprotein A2/B1 RNA or any combination thereof;

b) amplifying or signal amplifying said fraction of the extracted RNA or corresponding cDNA prepared therefrom, wherein amplification is performed [in] either [a] qualitatively or quantitatively [fashion] using primers or probes specific for the tumor-derived or tumor-associated RNA or cDNA corresponding thereto to produce an amplified product; and

c) detecting the amplified product produced from the RNA or cDNA.

2. (Amended) A method for detecting extracellular tumor-derived or tumor-associated RNA in a non-cellular fraction of a bodily fluid from a human or animal, wherein the tumor-derived or tumor-associated RNA is epidermal growth factor RNA, epidermal growth factor receptor (~~erb-B-1~~) RNA, her-2/neu RNA, c-myc RNA, heterogeneous nuclear ribonucleoprotein A2/B1 RNA or any combination thereof, the method comprising the steps of:

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- a) extracting mammalian total RNA from a non-cellular fraction of a bodily fluid, wherein a fraction of said extracted RNA comprises an extracellular tumor-derived or tumor-specific RNA species that is epidermal growth factor RNA, epidermal growth factor receptor (erb-B-1) RNA, her-2/neu RNA, c-myc RNA, heterogeneous nuclear ribonucleoprotein A2/B1 RNA or any combination thereof;
- b) amplifying or signal amplifying said fraction of the extracted RNA or cDNA corresponding thereto, wherein amplification is performed [in] either [a] qualitatively or quantitatively [fashion] using primers or probes specific for the tumor-derived or tumor-associated RNA or cDNA corresponding thereto to produce an amplified product; and
- c) detecting the amplified product produced from the RNA or cDNA corresponding thereto.

8. (Amended) The method of claim 2, wherein the RNA in step (a) is extracted from a non-cellular fraction of a bodily fluid using an RNA extraction method that is a gelatin extraction method; silica, glass bead, or diatom extraction method; guanidine-thiocyanate-phenol solution extraction method; guanidinium thiocyanate acid-based extraction method; phenol-chloroform-based extraction method; or involves centrifugation through a cesium chloride or similar gradient.

9. (Amended) The method for screening an animal or human for malignancy or premalignancy associated with epidermal growth factor RNA, epidermal growth factor receptor (erb-B-1) RNA, her-2/neu RNA, c-myc RNA, or heterogeneous nuclear ribonucleoprotein A2/B1 RNA or any combination thereof, the method comprising the steps of performing the method of claim 1 qualitatively or quantitatively, and detecting a product produced by said RNA in the plasma or serum of said animal or human,

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wherein detection of said RNA indicates that malignant or premalignant cells are present in the body of said animal or human.

10. (Amended) The method for screening an animal or human for malignancy or premalignancy associated with epidermal growth factor RNA, epidermal growth factor receptor (erb-B-1) RNA, her-2/neu RNA, c-myc RNA, or heterogeneous nuclear ribonucleoprotein A2/B1 RNA or any combination thereof, the method comprising the steps of performing the method of claim 2 qualitatively or quantitatively, and detecting a product produced by said RNA in the plasma or serum of said animal or human, wherein detection of said RNA indicates that malignant or premalignant cells are present in the body of said animal or human.

21. (Amended) A method for monitoring an animal or human for a malignant or premalignant disease, wherein the malignant or premalignant disease is associated with a tumor-derived or tumor-associated RNA that is epidermal growth factor RNA, epidermal growth factor receptor (erb-B-1) RNA, her-2/neu RNA, c-myc RNA, or heterogeneous nuclear ribonucleoprotein A2/B1 RNA, or any combination thereof, the method comprising the step of:

(1) detecting RNA associated with the malignant or premalignant disease qualitatively or quantitatively , wherein the RNA is epidermal growth factor RNA, epidermal growth factor receptor (erb-B-1) RNA, her-2/neu RNA, c-myc RNA, or heterogeneous nuclear ribonucleoprotein A2/B1 RNA or any combination thereof, according to a method comprising the steps of:]

a) extracting mammalian total RNA from plasma or serum, wherein a fraction of said extracted RNA comprises epidermal growth factor RNA, epidermal

growth factor receptor (*erb-B-1*) RNA, her-2/neu RNA, c-myc RNA, heterogeneous nuclear ribonucleoprotein A2/B1 RNA or any combination thereof;

b) amplifying or signal amplifying said fraction of the extracted RNA or corresponding cDNA, wherein amplification is performed qualitatively or quantitatively using primers or probes specific for the tumor-derived or tumor-associated RNA or cDNA corresponding thereto, to produce an amplified product; and

c) detecting the amplified product produced from RNA or cDNA corresponding thereto.

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37. (Amended) A method according to claim 1, further comprising the step of performing a diagnostic test for diagnosing cancer or premalignancy when epidermal growth factor RNA, epidermal growth factor receptor (*erb-B-1*) RNA, her-2/neu RNA, c-myc RNA, heterogeneous nuclear ribonucleoprotein A2/B1 RNA or any combination thereof is detected in plasma or serum of an animal or human.

40. (Amended) A method for monitoring response to an anticancer therapy, comprising the step of performing the method of claim 1 on blood plasma or serum from an animal or human with cancer to whom anticancer therapy is administered, and wherein response to the anticancer therapy is accomplished by qualitative or quantitative detection of epidermal growth factor RNA, epidermal growth factor receptor (*erb-B-1*) RNA, her-2/neu RNA, c-myc RNA, heterogeneous nuclear ribonucleoprotein A2/B1 RNA or any combination thereof.

41. (Amended) A method for monitoring response to an anticancer therapy, comprising the step of performing the method of claim 1 on blood plasma or serum from an animal or human with cancer to whom anticancer therapy is administered, and

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wherein response to the anticancer therapy is accomplished by qualitative or quantitative detection of epidermal growth factor RNA, epidermal growth factor receptor (*erb-B-1*) RNA, her-2/neu RNA, c-myc RNA, heterogeneous nuclear ribonucleoprotein A2/B1 RNA or any combination thereof.

51. (Amended) A diagnostic kit comprising primers specific for amplifying heterogeneous nuclear ribonucleoprotein A2/B1 RNA or cDNA prepared therefrom and reagents for extracting total RNA from an acellular fraction of a bodily fluid according to the method of claim 2.

52. (Amended) A method for producing cDNA by reverse transcription of a fraction of extracellular mammalian total RNA extracted from plasma or serum, wherein the fraction comprises epidermal growth factor RNA, epidermal growth factor receptor (*erb-B-1*) RNA, her-2/neu RNA, c-myc RNA, heterogeneous nuclear ribonucleoprotein A2/B1 RNA, or any combination thereof, whereby cDNA corresponding to said RNA is produced.

53. (Amended) A method for producing cDNA by reverse transcription of a fraction of extracellular mammalian RNA extracted from an acellular fraction of a bodily fluid, wherein the fraction comprising epidermal growth factor RNA, epidermal growth factor receptor (*erb-B-1*) RNA, her-2/neu RNA, c-myc RNA, heterogeneous nuclear ribonucleoprotein A2/B1 RNA, or any combination thereof, whereby cDNA corresponding to said RNA is produced.

"Clean" copy of amended claims

1. (Twice amended) A method for detecting tumor-derived or tumor-associated RNA in the plasma or serum fraction of blood from a human or animal, wherein the tumor-derived or tumor-associated RNA is epidermal growth factor RNA, epidermal growth factor receptor RNA, her-2/neu RNA, c-myc RNA, heterogeneous nuclear ribonucleoprotein A2/B1 RNA or any combination thereof, the method comprising the steps of:
 - a) extracting total RNA from plasma or serum from a human or animal, wherein a fraction of said extracted RNA comprises a tumor-derived or tumor-specific RNA species that is epidermal growth factor RNA, epidermal growth factor receptor RNA, her-2/neu RNA, c-myc RNA, heterogeneous nuclear ribonucleoprotein A2/B1 RNA or any combination thereof;
 - b) amplifying or signal amplifying said fraction of the extracted RNA or corresponding cDNA prepared therefrom, wherein amplification is performed either qualitatively or quantitatively using primers or probes specific for the tumor-derived or tumor-associated RNA or cDNA corresponding thereto to produce an amplified product; and
 - c) detecting the amplified product produced from the RNA or cDNA.
2. (Twice amended) A method for detecting extracellular tumor-derived or tumor-associated RNA in a non-cellular fraction of a bodily fluid from a human or animal, wherein the tumor-derived or tumor-associated RNA is epidermal growth factor RNA, epidermal growth factor receptor RNA, her-2/neu RNA, c-myc RNA, heterogeneous nuclear ribonucleoprotein A2/B1 RNA or any combination thereof, the method comprising the steps of:

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- a) extracting total RNA from a non-cellular fraction of a bodily fluid from a human or animal, wherein a fraction of said extracted RNA comprises an extracellular tumor-derived or tumor-specific RNA species that is epidermal growth factor RNA, epidermal growth factor receptor RNA, her-2/neu RNA, c-myc RNA, heterogeneous nuclear ribonucleoprotein A2/B1 RNA or any combination thereof;
- b) amplifying or signal amplifying said fraction of the extracted RNA or cDNA corresponding thereto, wherein amplification is performed either qualitatively or quantitatively using primers or probes specific for the tumor-derived or tumor-associated RNA or cDNA corresponding thereto to produce an amplified product; and
- c) detecting the amplified product produced from the RNA or cDNA corresponding thereto.

3. (Amended) The method of claim 1, wherein the amplification in step (b) is performed by a RNA amplification method that is reverse transcriptase polymerase chain reaction, ligase chain reaction, branched DNA signal amplification, amplifiable RNA reporters, Q-beta replication, transcription-based amplification, isothermal nucleic acid sequence-based amplification, self-sustained sequence replication assay, boomerang DNA amplification, strand displacement activation, or cycling probe technology.

4. (Amended) The method of claim 2, wherein the amplification in step (b) is performed by a RNA amplification method that is reverse transcriptase polymerase chain reaction, ligase chain reaction, branched DNA signal amplification, amplifiable RNA reporters, Q-beta replication, transcription-based

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amplification, isothermal nucleic acid sequence-based amplification, self-sustained sequence replication assay, boomerang DNA amplification, strand displacement activation, or cycling probe technology.

5. (Amended) The method of claim 1, wherein detection of the amplified product in step (c) is performed using a detection method that is gel electrophoresis, capillary electrophoresis, Southern blot analysis, Northern blot analysis, reverse blot detection, high-performance liquid chromatography, or enzyme-linked immunosorbent assay (ELISA) using biotinylated or other modified primers, labeled fluorescent or chromagenic probes, or laser-induced fluorescence detection.
6. (Amended) The method of claim 2, wherein detection of the amplified product in step (c) is performed using a detection method that is gel electrophoresis, capillary electrophoresis, Southern blot analysis, Northern blot analysis, reverse blot detection, high-performance liquid chromatography, or enzyme-linked immunosorbent assay (ELISA) using biotinylated or other modified primers, labeled fluorescent or chromagenic probes, or laser-induced fluorescence detection.
7. The method of claim 1, wherein the RNA in step (a) is extracted from plasma or serum using an RNA extraction method that is a gelatin extraction method; silica, glass bead or diatom extraction method; guanidine-thiocyanate-phenol solution extraction method; guanidinium thiocyanate acid-based extraction method; phenol-chloroform-based extraction method; or involves centrifugation through a cesium chloride or similar gradient.

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8. (Amended) The method of claim 2, wherein the RNA in step (a) is extracted from a non-cellular fraction of a bodily fluid using an RNA extraction method that is a gelatin extraction method; silica, glass bead, or diatom extraction method; guanidine-thiocyanate-phenol solution extraction method; guanidinium thiocyanate acid-based extraction method; phenol-chloroform-based extraction method; or involves centrifugation through a cesium chloride or similar gradient.
9. (Twice amended) The method for screening an animal or human for malignancy or premalignancy associated with epidermal growth factor RNA, epidermal growth factor receptor RNA, her-2/neu RNA, c-myc RNA, or heterogeneous nuclear ribonucleoprotein A2/B1 RNA or any combination thereof, the method comprising the steps of performing the method of claim 1, wherein detection of said RNA indicates that malignant or premalignant cells are present in the body of said animal or human.
10. (Twice amended) The method for screening an animal or human for malignancy or premalignancy associated with epidermal growth factor RNA, epidermal growth factor receptor RNA, her-2/neu RNA, c-myc RNA, or heterogeneous nuclear ribonucleoprotein A2/B1 RNA or any combination thereof, the method comprising the steps of performing the method of claim 1 wherein detection of said RNA indicates that malignant or premalignant cells are present in the body of said animal or human.
11. (Amended) A method according to claim 9 wherein the animal is a human.
12. (Amended) A method according to claim 10 wherein the animal is a human.

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21. (Amended) A method for monitoring an animal or human for a malignant or premalignant disease, wherein the malignant or premalignant disease is associated with a tumor-derived or tumor-associated RNA that is epidermal growth factor RNA, epidermal growth factor receptor RNA, her-2/neu RNA, c-myc RNA, or heterogeneous nuclear ribonucleoprotein A2/B1 RNA, or any combination thereof, the method comprising the step of:

- a) extracting total RNA from plasma or serum from a human or animal, wherein a fraction of said extracted RNA comprises epidermal growth factor RNA, epidermal growth factor receptor RNA, her-2/neu RNA, c-myc RNA, heterogeneous nuclear ribonucleoprotein A2/B1 RNA or any combination thereof;
- b) amplifying or signal amplifying said fraction of the extracted RNA or corresponding cDNA, wherein amplification is performed qualitatively or quantitatively using primers or probes specific for the tumor-derived or tumor-associated RNA or cDNA corresponding thereto, to produce an amplified product; and
- c) detecting the amplified product produced from RNA or cDNA corresponding thereto.

36. A method according to claim 1, further comprising the step of performing a diagnostic test for diagnosing cancer or premalignancy when epidermal growth factor RNA, epidermal growth factor receptor RNA, her-2/neu RNA, c-myc RNA, heterogeneous nuclear ribonucleoprotein A2/B1 RNA or any combination thereof is detected in plasma or serum of an animal or human.

37. (Twice amended) A method according to claim 1, further comprising the

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step of performing a diagnostic test for diagnosing cancer or premalignancy when epidermal growth factor RNA, epidermal growth factor receptor RNA, her-2/neu RNA, c-myc RNA, heterogeneous nuclear ribonucleoprotein A2/B1 RNA or any combination thereof is detected in plasma or serum of an animal or human.

40. (Amended) A method for monitoring response to an anticancer therapy, comprising the step of performing the method of claim 1 using blood plasma or serum from an animal or human with cancer to whom anticancer therapy is administered, and wherein response to the anticancer therapy is accomplished by qualitative or quantitative detection of epidermal growth factor RNA, epidermal growth factor receptor RNA, her-2/neu RNA, c-myc RNA, heterogeneous nuclear ribonucleoprotein A2/B1 RNA or any combination thereof.

41. (Twice amended) A method for monitoring response to an anticancer therapy, comprising the step of performing the method of claim 1 using an acellular fraction of a bodily fluid from an animal or human with cancer to whom anticancer therapy is administered, and wherein response to the anticancer therapy is accomplished by qualitative or quantitative detection of epidermal growth factor RNA, epidermal growth factor receptor RNA, her-2/neu RNA, c-myc RNA, heterogeneous nuclear ribonucleoprotein A2/B1 RNA or any combination thereof.

52. (Twice amended) A method for producing cDNA by reverse transcription of a fraction of extracellular total RNA extracted from plasma or serum from a human or animal, wherein the fraction comprises epidermal growth factor RNA, epidermal growth factor receptor RNA, her-2/neu RNA, c-myc RNA,

heterogeneous nuclear ribonucleoprotein A2/B1 RNA, or any combination thereof, whereby cDNA corresponding to said RNA is produced.

53. (Twice amended) A method for producing cDNA by reverse transcription of a fraction of extracellular total RNA extracted from an acellular fraction of a bodily fluid from a human or animal, wherein the fraction comprising epidermal growth factor RNA, epidermal growth factor receptor RNA, her-2/neu RNA, c-myc RNA, heterogeneous nuclear ribonucleoprotein A2/B1 RNA, or any combination thereof, whereby cDNA corresponding to said RNA is produced.